Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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The Medicines and Healthcare products Regulatory Agency is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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This month, we inform you of a case of fatal progressive multifocal leukoencephalopathy in a multiple sclerosis patient who had severe, prolonged lymphopenia while taking dimethyl fumarate. While the case is being further investigated, we remind you to monitor patients by checking full blood counts (including lymphocytes) before prescribing dimethyl fumarate and then every 6 to 12 months. Stop treatment immediately if you suspect progressive multifocal leukoencephalopathy—see page 2.

The licence-holder of ferumoxytol (Rienso) intravenous iron has voluntarily withdrawn it from the UK market for commercial reasons. Please see the drug recall sent on 12 March 2015—see page 3.

We have launched our new online learning module on corticosteroids to help clinicians understand how to recognise, manage and avoid the important side effects of these valuable and widely prescribed medicines. The learning module has been approved for up to 2 continuing professional development (CPD) credits—see page 3.

Finally, if you are concerned about advertising you see for a medicine, please report it—see page 3.

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1 **Dimethyl fumarate (Tecfidera): fatal PML in an MS patient with severe, prolonged lymphopenia**

Check full blood counts (including lymphocytes) before prescribing dimethyl fumarate and then every 6 to 12 months. Stop treatment immediately if you suspect progressive multifocal leukoencephalopathy.

Before prescribing dimethyl fumarate:

- ensure that the full blood count (including lymphocytes) has been checked - note that dimethyl fumarate has not been studied in patients with pre-existing lymphopenia or in combination with other immunosuppressive medicines
- explain the risk of lymphopenia and potential risk of progressive multifocal leukoencephalopathy (PML) to patients and carers – see link in "further information" below

During dimethyl fumarate treatment:

- monitor patients - check full blood counts, including lymphocytes, every 6 to 12 months or more frequently if clinically indicated
- monitor patients with lymphopenia closely for features of PML (eg signs and symptoms of neurological dysfunction) and other opportunistic infections
- stop dimethyl fumarate treatment immediately and investigate appropriately if you suspect PML
- consider that PML can present with similar features to multiple sclerosis because PML is also a demyelinating disease
- continue to report suspected adverse drug reactions to dimethyl fumarate or any other medicine on a Yellow Card: www.gov.uk/yellowcard

Dimethyl fumarate is licensed to treat relapsing remitting multiple sclerosis in adults. Dimethyl fumarate can cause severe lymphopenia: lymphocyte counts decreased by approximately 30% from baseline values during treatment in clinical trials.

PML case details

A fatal case of PML was reported in Germany in October 2014 in a patient participating in the open-label ENDORSE study of dimethyl fumarate in multiple sclerosis. The patient received dimethyl fumarate for 4.5 years and experienced severe lymphopenia for more than 3.5 years.

This is the only known case of PML associated with dimethyl fumarate in a multiple sclerosis patient to date. Cases of PML have been reported with the use of fumaric acid esters (including dimethyl fumarate) in lymphopenic patients with psoriasis. However, in some of these cases, it could not be confirmed that the treatment caused PML (eg other risk factors for PML may have been present).

PML and multiple sclerosis symptoms can be similar

PML can present with similar features to multiple sclerosis as both are demyelinating diseases.[1] Advise patients to consult their prescriber if they notice any new, unusual or worsening symptoms.

Unlicensed use of dimethyl fumarate for psoriasis

Medicines containing dimethyl fumarate and other fumaric acid esters are not licensed in the UK for use in psoriasis. However, we are aware that these medicines are sometimes imported as "specials".[2] If you are considering such use, be aware of the risks of severe, prolonged lymphopenia and serious opportunistic infections.

Regulatory action

The licence-holder is working with the European Medicines Agency to evaluate the evidence for the risk of PML and to consider changes to the prescribing information. We will communicate any new advice for healthcare professionals as soon as it is finalised.

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References

1. Ludwig Kappos and others. 'Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring' Lancet Neurology 2011: volume 10, pages 745-758
2. British Association of Dermatologists. 'Fumaric acid esters' information for patients, August 2013

Further information

Letter sent to healthcare professionals in December 2014- https://assets.digital.cabinet-office.gov.uk/media/5510375240f0b61404000010/Tecfidera_DHPC_sent_3Dec2014.pdf

Dimethyl fumarate summary of product characteristics http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002601/WC500162069.pdf

Information to give to patients and carers https://assets.digital.cabinet-office.gov.uk/media/55159c5ee5274a142b000067/Dimethyl_fumarate_patient_info_March_2015.pdf

NICE guidance TA320 – Dimethyl fumarate for treating relapsing-remitting multiple sclerosis http://www.nice.org.uk/guidance/ta320

NICE evidence search – Fumaderm: what is the evidence for its efficacy and safety in treating psoriasis? https://www.evidence.nhs.uk/document?ci=http%3a%2f%2fwww.medicinesresources.nhs.uk%2fGetDocument.aspx%3fpageId%3d514045%3ffromsource%3dnelm&returnUrl=Search%3fq%3dfumaderm%2band%2bevidence%2bfor%2buse&q=fumaderm+and+evidence+for+use

2 **Ferumoxytol (Rienso) intravenous iron no longer available for use**

Ferumoxytol recall:
https://assets.digital.cabinet-office.gov.uk/media/55159aa7ed915d142400005f/Rienso_DHPC_sent_13_March_2015.pdf

The licence-holder of ferumoxytol has voluntarily withdrawn it from the UK market for commercial reasons. Please see the drug recall sent on 12 March 2015.

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3 **Corticosteroids e-learning module launched**

Corticosteroids learning module:
https://www.gov.uk/government/publications/e-learning-modules-medicines-and-medical-devices/e-learning-modules-medicines-and-medical-devices#corticosteroids

The new module helps clinicians understand how to identify, manage and avoid the important side effects of these valuable and widely prescribed medicines—vital knowledge for optimising the use of corticosteroids.

The interactive module is presented on our dedicated platform for tracking and organising learning. Designed for clinical practitioners, the module covers:

- recognition of commonly used corticosteroids
- important corticosteroid adverse effects
- factors that increase the risk of adverse effects
- how clinicians and patients can reduce the risk
- specific treatment of the adverse effect

Used with authoritative clinical information and treatment guidelines, this module is a key practical aid to doctors, pharmacists and nurses.

The module incorporates interactive knowledge-check exercises to consolidate learning. You will be able to download evidence of your learning on successfully completing an assessed quiz.

E-learning modules page
https://www.gov.uk/government/publications/e-learning-modules-medicines-and-medical-devices/e-learning-modules-medicines-and-medical-devices

The learning module on corticosteroids has been approved for up to 2 continuing professional development (CPD) credits by the Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the United Kingdom.

Access the full range of MHRA learning modules on the e-learning modules page (see left).

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4 **Report misleading medicines advertisements**

If you are concerned about advertising you see for a medicine, please report it to MHRA or the industry self-regulatory body.

Further information
MHRA Blue Guide,
https://www.gov.uk/government/collections/how-to-advertise-and-promote-medicines

MHRA Advertising Standards annual report 2014
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/406523/Advertising_Standards_9th_Annual_Report.pdf

ABPI Code of Practice
http://www.pmcpa.org.uk/thecode/Pages/default.aspx
E-learning for healthcare professionals
http://www.pmcpa.org.uk/training/Pages/E-learning-for-health-professionals.aspx

By law, advertising for a medicine must:

- comply with the medicine's summary of product characteristics (licence)
- promote the rational use of the product by presenting it objectively and without exaggerating its properties
- not mislead

There are also legal and self-regulatory requirements covering gifts and payments made by the pharmaceutical industry to healthcare professionals. These requirements apply to receipt of as well as giving of gifts and inducements. New self-regulatory requirements came into effect this year for disclosure of transfers of value.

MHRA and the industry self-regulatory body, the Prescription Medicines Code of Practice Authority (PMCPA), investigate complaints about breaches of these requirements. If you have a concern about advertising for a medicine, please help to ensure effective regulation by reporting it to PMCPA at complaints@pmcpa.org.uk or the MHRA at advertising@mhra.gsi.gov.uk.

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